caused by conducting trials in developing nations. It may be just a matter of time before the USA decides to uphold the revised Declaration of Helsinki or challenge it.

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Of silicon and submarines

Whether it be in the world's smallest pharmaceutical plants, computer factories or dockyards, engineers need look no further than biology for future solutions

The application of nanotechnology to biological concepts is a particularly interesting subject; on the one hand it allows biologists to analyse the physical properties of biological molecules using nano techniques (Moore, 2001), while on the other it exploits these very molecules as miniature machines. After all, the most successful nanomachines ever created are those operating inside every cell. The properties and construction of complex self-assembling biological molecules are providing scientists with important insights into how to create their own nanomachines, or better still, modify existing ones to take on new tasks.

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'The fastest way to utilise nanotechnology is to build on the machines existing in nature,' noted Carlo Montemagno, in describing the principle of his work at Cornell University in Ithaca, NY. His pet machine is the F_1F_0 ATPase, a far more efficient machine than any human engineer could expect to make. It should be possible to use this to make 'nano-pumps', intracellular concentrating machines that selectively pump molecules into a cellular compartment and sequester them, according to Montemagno. This may seem far-fetched, but obviously not to the National Science Foundation, which provides the funding. Already Montemagno is working on an *in vitro* sorting system, the goal being to produce human cell lines that express and assemble the pump motors—engineered variants of the bacillus ATPase—into the sorting compartment (Figure 1). Moreover, he plans to construct an artificial minimal cell to produce the

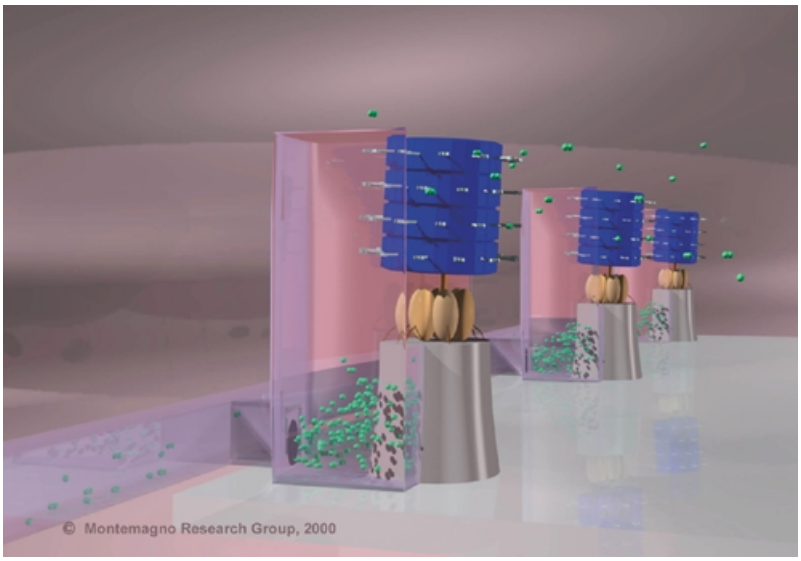

Fig. 1. A sorting device based on the the bacterial F_1F_0 ATPase could pump compounds into a harvesting compartment in a eukaryotic cell.

components of the sorting machine, which could be the starting point for cell-sized chemical production plants. As Montemagno remarked, with a measure of caution and modesty—for he knows what damage hype can do to science—'the long-term focus is to make machines that are fully integrated with the life process.' At present, this research is at the 'foundation technology' level, a stage that he likened to the discovery that 'we can put electricity through a wire.' But in 10 years, the Cornell scientist thinks, 'it may be possible to have machines that do ultra-pure and high capacity chemical production.'

Indeed, their effectiveness and versatility make biological machines and structures not only useful little helpers in the synthesis of organic molecules but in the computer industry as well. The computer chip producers suffer from the effect of Moore's laws, which state that the rate of miniaturisation increases exponentially with time while the cost of the fabrication plant increases exponentially with miniaturisation. 'If Moore's first law doesn't kill you, his second law will,' remarked Andrew Turberfield from the Department of Physics at the University of Oxford, UK. So those hard-wired technologists who are convinced that they will find some solution to the rapidly approaching size limit might have to look to biological solutions soon. According to Turberfield, it will be DNA that replaces the current silicon-based method of computer chip production. 'I'm enjoying the opportunity to use archetypal biological material for engineering purposes,' Turberfield mused, clearly fascinated by the link between these seemingly unrelated fields. Though the research is not close to application, rather in the proof of principle stage, the Oxford professor clearly considers DNA an eminently suitable structural material. The two most likely applications would be the use of molecular recognition between complementary DNA strands to arrange entities in three dimensions, and DNA hybridisation as an energy source to drive a molecular machine.

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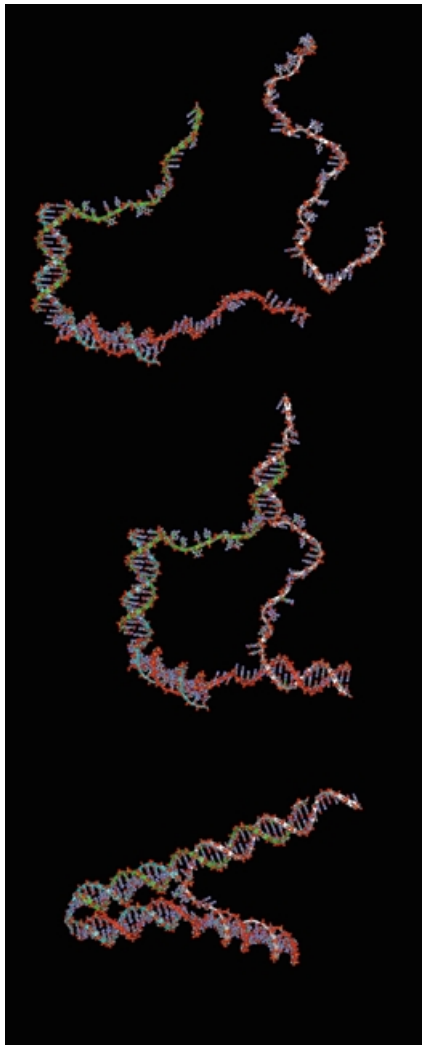

Fig. 2. A pair of molecular tweezers; adding a complementary strand of DNA closes the tweezers, which can be reopened by adding a second complementary strand to release the first.

The latter was the subject of a *Nature* paper (Yurke *et al.*, 2000) in which Turberfield and colleagues demonstrated a pair of DNA 'tweezers'. These could be closed and opened by hybridising complementary DNA strands with single-stranded overhangs at the ends (Figure 2). This can be thought of as a machine idling, but the force it generates, typically 10 pN, could be used to drive something, thinks Turberfield, who credits his co-researcher Berhard Yurke from Lucent Technologies with much of the work. At present, the DNA machine can only turn over by sequentially adding complementary strands. However, the aim is to create a system where the two types of 'fuel' strands coexist, hence producing a free-running machine.

Turberfield envisages series of such machines assembled on a substrate, acting as a conveyor belt or molecular assembly line for making computer components that would swim in a bulk solution of raw materials labelled with oligonucleotides. The machinery would identify individual components by their labels, and assemble them into the final product. This vision is shared by Gunter von Kiedrowski, Professor of Organic Chemistry at the Ruhr University in Bochum, Germany. His group makes DNA scaffolds (Scheffler *et al.*, 1999), which could be used for spatially arranging enzymes to make processive multi-enzyme complexes, a particularly interesting prospect for the chemical industry.

DNA—the embodiment of information-processing material—could one day challenge the silicon chip

In a proof of principle experiment, von Kiedrowski has already made molecular tetrahedrons that arrange gold particles in three dimensions (Figure 3).

Whereas classical approaches to using organic molecules in inorganic systems have concentrated on covalent bonds, the DNA constructions rely entirely on non-covalent interactions. Their size can be controlled by the rate at which they condense in solution, a kinetic parameter dependent on the rate of cooling. Like many others in the field, von Kiedrowski believes that biology is best. 'Drexler and those visionaries of nanotechnology have a rather mechanical view of doing things, but biology doesn't do things by robots,' he said, 'it self-organises.' He also sees that DNA—the embodiment of information-processing material—could one day challenge the silicon chip. 'One could also conceive of applications in DNA computing, e.g. the solving of the so-called travelling salesman problem, and cryptology,' von Kiedrowski said. One of the first places the public could encounter this technology is in certification and tagging, where a specific sequence of DNA would be used to uniquely mark a product as genuine. At present this is too

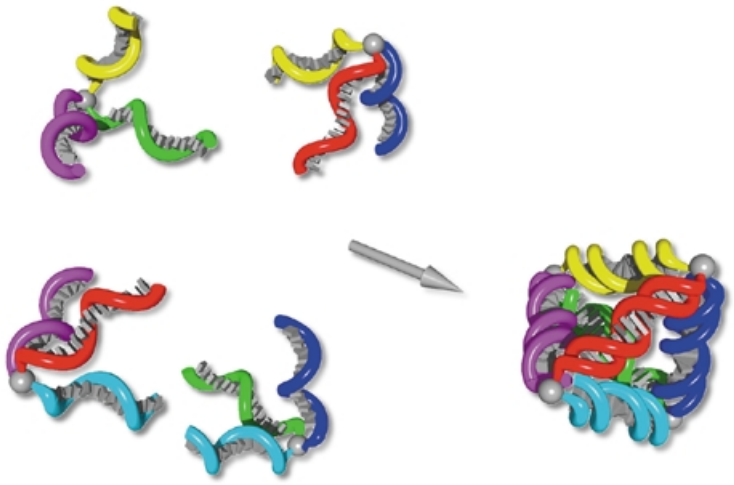

Fig. 3. Complementary DNA sequences to organise small objects in three dimensions.

expensive for companies to adopt, but according to von Kiedrowski it could be only 2–3 years away, especially since the prices of large-scale DNA synthesis are dropping.

No doubt some of the most important applications will be in medicine. And nothing tickles the media's fancy more than nanosubmarines patrolling the blood to identify and attack bacteria, viruses, cancer cells and other alien beings. Here, classical submarine-building techniques appear to be in the lead over biological approaches. One of the dockyards is at microTEC, a company in Duisburg, Germany. Though it should properly be described as a micro- or even milli-, rather than a nano-submarine—the hull has dimensions of 650 µm × 4 mm—it claims to be small enough to reach parts of the body that invasive techniques cannot satisfactorily reach. A prototype with a marine propeller of 600 µm diameter was displayed at Expo 2000 in Hannover (Figure 4). However, as Andrea Reinhardt, CEO at microTEC, explained, this was more a concept craft designed to communicate the idea to the public. In reality, she said, the submarines would not be driven by a propeller, as that would damage red blood cells; rather they would circulate as passive containers with sensors and drug delivery devices.

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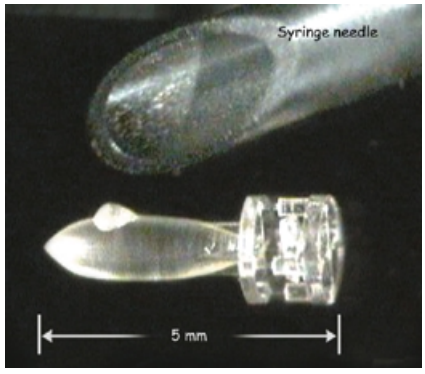

Fig. 4. The microTEC micro-sub presented at the Expo 2000 in Hannover.

Such a 'smart pill', as it has been christened, might make its first appearance in the diagnosis and treatment of stomach ailments that lead to cancer, thinks Reinhardt. The pill (Figure 5) 'would be directed, and recognise the right place for drug delivery by sensing pH,' she said. Other smart capsules could be injected into the bloodstream and travel to tumour sites, where they would deliver a therapeutic dose of radiation. Working with clinicians, microTEC is primarily developing approaches to boldly go where no classical endoscope has gone before. The limiting step for such devices is the miniaturisation and packaging of the sensor electronics for diagnosis and the mechanism for drug release.

Nature, it appears, has already made the right drug delivery vessel in the form of the HK97 bacteriophage. Researchers at the Scripps Research Institute in Pittsburgh, PA, have found features of the viral capsid that make it an interesting device for drug delivery (Wikoff *et al.*, 2000). In addition to covalent interactions, HK97's capsid proteins are held together by 420 isopeptide bonds, which produce an inter-linked ring structure reminiscent of chainmail. In the immature capsid, there are 'reasonable sized pores through which peptides escape during maturation,' noted the first author researcher, Bill Wikoff. These then close as the capsid matures, a process that can be mimicked *in vitro* simply by lowering the pH. The mature viral capsid is remarkably resistant to heat, proteases and chemical solvents, thus making it an ideal drug container. Wikoff imagines that small peptides or other organic molecules could be diffused into the capsid in its 'open' form, and released later at their target. However, the problem of how to get the drug out again will tax the imagination a little more. Wikoff thinks this could be achieved

The rate-limiting step to developing devices that can reach sites where classical endoscopy cannot go is the miniaturisation and packaging of sensor electronics

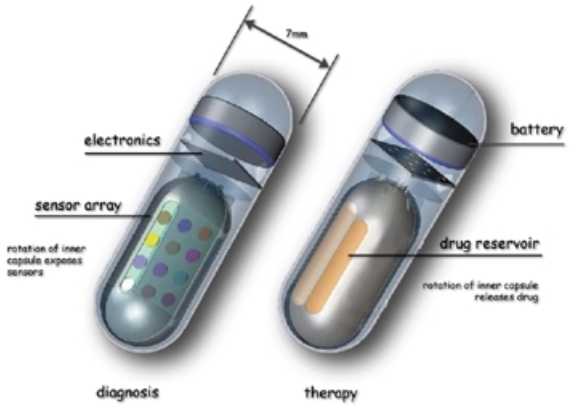

Fig. 5. The microTEC smart pills.

by incorporating a protease into the capsid. Then one could conceive of a man-made mini-sub armed with drug-containing virus particles in its torpedo tubes.

The prospect of using biological structures to build nanomachines is indeed fascinating, but with it comes a danger of hype and fraud. Last year, the conning tower of a 'bug-propelled submarine' surfaced in Utah with a masters student named Eldrid Sequeira at the controls. Before it was sunk by the torpedo of reality, this conceptually fascinating little U-boat wreaked havoc with the press, not to mention causing Sequeira's professor considerable embarrassment. As a source at the University of Utah commented, 'Eldrid's roommate is a biology student and the two of them began discussing the idea of bacteria-powered submarines and their possible uses.' The idea consisted of a container that houses a bacterially driven rotor—either whole bacteria or simply their flagellar motors attached to radial vanes—which turns a drive shaft, which exits the container via a bearing and ends in a classical marine propeller. One can only imagine that so confident were they, having practically built the thing—albeit in their heads—that they went ahead with press releases and interviews. Reports in *New Scientist*, the BBC news and *TIME* magazine heralded the 'bug-propelled' submarine. Unfortunately, as the Utah source pointed out, 'this is not part of Eldrid's master's degree program and research,' just an idea. It would be unfortunate if research on more serious ideas in this exciting field were damaged by such nano-hype.

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